from baculoviral vectors, adenoviral vectors and adeno-associated viral vectors.

5. (Amended) A method according to claim 3, wherein said vector is an adenoviral vector.

REMARKS

Reconsideration is requested.

Claims 1 to 10 are pending.

Return of an initialed copy of the PTO 1449 Form filed November 7, 2000 is requested, pursuant to MPEP § 609. A further copy of the PTO 1449 Form is attached.

The Examiner's comment regarding the certified copy of the priority document is noted however the attached FORM PTO/DO/EO/903 confirm the certified copy of the priority document has been received by the U.S. Patent Office and a further copy of the same should not be required. Acknowledgement of the same is requested in the Examiner's next Action.

The Specification has been amended to include the attached Abstract, as required by the Examiner. Withdrawal of the objection to the specification based on the same is requested. The attached Abstract is the same as the published Abstract of the published PCT application. No new matter has been added.

The Section 112, second paragraph, rejection of claims 2, 4 and 5, is obviated by the above amendments. Reconsideration and withdrawal of the rejection are requested.

The Section 103 rejection of claims 1 to 10, over WO 96/09373 (Watt et al.) in view of Choi (1990, PNAS, Vol. 87, 7988-7992) and Murry (1995, FASEB, Vol. 9, No. 4, A883) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

Watt et al. describe a method of treatment of muscular disorders in a patient, which comprises administering to or adjacent to the muscle cells of the patient immunologically compatible dermal fibroblast cells under conditions effective to convert the dermal fibroblast cells to myogenic cells. See, claim 1, page 23 of Watt. In the

conditions described by Watt et a!., myogenic conversion, i.e., the process by which a fibroblast becomes a myogenic cells and makes new muscle, is intended to occur spontaneously upon injection into the muscle of the patient. Spontaneous myogenic conversion however, occurs at a very low frequency, its outcome is unpredictable, and it is of no practical use as a therapeutic intervention. No therapy for muscular dystrophies has ever been known to have developed based on such a low-efficiency technology. Watt et a!. do not teach how to increase the frequency of myogenic conversion of fibroblasts to a level that would make it practically usable in a clinical setting. As such, the method described by Watt et a!. cannot be practiced by a person having ordinary skill in the art in order to cure or treat a muscle disorder.

The presently claimed invention provides a method of using fibroblasts as a source of muscle cells and the use of a *high-efficiency, non-integrating viral vector* to achieve transient expression of a muscle-determination gene, for example myoD, in an in vitro culture.

Choi et al. may describe that the expression of myoD into dermal fibroblasts induces their conversion into muscle cells. However, Choi et a!. use an integrating retroviral vector, which implies the permanent acquisition of the gene by the transduced fibroblasts. Due to the combination of the low efficiency of gene transfer obtained with this type of vectors, and the anti-proliferative action of the permanently acquired myoD gene, the efficiency of myogenic conversion obtained by the method described by Choi et al. is in the range of 1 to 5% (page 798, right column, line 8). This efficiency is not significantly different from that obtained by the spontaneous conversion described by Watt et al., and is again of no practical use.

The applicants respectfully submit that Murry et al. does not anticipate an increased efficiency of fibroblast conversion by using an adenoviral vector to deliver myoD into the fibroblasts. Initially, the applicants note that in their abstract, Murry et al., use *cardiac* fibroblast as a source of cells for their specific application, i.e., improvement of the *heart muscle* function. Moreover, they do not give any specific frequency for their in vitro conversion. On the contrary, they admit a very poor myogenic conversion of these particular cells upon in vivo delivery of the vector. The possibility of delivering the gene directly into the heart was in fact the reason why they chose an adenoviral vector

in the first place. In practical terms, the results of Murry et al do not predict or imply or suggest that the use of an adenoviral vector might improve the efficiency of myogenic conversion of *dermal* fibroblasts in culture for the specific purpose of *skeletal muscle* implantation. As a matter of fact, although the publication of Choi et a!. and Murray et a!. precede that of Watt et al. by more than five years and one year respectively, Watt et al. do not consider using myoD delivered by a retroviral or an adenoviral vector as a specific embodiment or a formulation to improve the characteristics of their invention.

The presently claimed invention is based on an entirely new concept, which is not suggested by the cited art. The presently claimed invention achieves myogenic conversion of dermal fibroblasts by *transient expression of high levels* of a muscle-determination gene, in particular myoD, with an adenoviral vector or a vector with comparable characteristics. The presently claimed method allows *massive,* i.e. more than 50%, conversion of fibroblasts ex vivo, resulting from both high efficiency of gene delivery to the cultured fibroblasts (more than 95%) and high efficiency of gene expression obtained by the high number of gene copies introduced into the cells by the non-integrating vector. Furthermore, since no integration of the gene into the genome of the fibroblasts is required, the cells can be used immediately after exposure to the transiently infecting vector, without any further culture steps such as those described by Choi et al., which invariably result in reduction of cell viability and cell aging. The difference is substantial and not merely technical: in order to be useful for therapeutic purposes, the majority of the injected fibroblasts must be converted to a muscle fate before, or upon, injection into the muscle tissue, and must engraft at high efficiency as they do under the conditions that the present applicants describe.

The fact that human fibroblast can be converted to muscle cells with such a high efficiency ex vivo was not obvious before the applicants' work described in the present specification. High efficiency was not considered by Watt et al. as a pre-requisite for the practical application of myogenic conversion. On the contrary, the applicants describe in both the above-identified specification, and in a subsequent publication (Lattanzi et al., J. Olin. Invest. 101: 2119-2128) that only high efficiency allows the practical use of converted dermal fibroblasts. The applicants therefore disagree with the Examiner's conclusion that an ordinarily skilled artisan would have had a reasonable expectation of

success based on the combined knowledge provided by Choi et al, Murry et al. and Watt et al.

For these reasons, the applicants submit that the overall concept of transient, high-level expression of a muscle-determination genes described and presently claimed is patentable over the cited art.

Withdrawal of the Section 103 rejection is requested.

In view of the above, the claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Should the Examiner feel that an interview with the undersigned would facilitate allowance of this application, the Examiner is encouraged to contact the undersigned.

Respectfully submitted,

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MARKED-UP COPY OF AMENDED CLAIMS

IN THE CLAIMS:

Amend the claims as follows:

2. (Amended) A method according to claim 1, wherein the therapeutic [therapeutical] gene is the dystrophin gene.

4. (Amended) A method according to claim 3, [wherein said viral vector is selected from baculovirus, adeno-related viruses, adeno-virus] wherein said vector is selected from baculoviral vectors, adenoviral vectors and adeno-associated viral vectors.

5. (Amended) A method according to claim 3, [wherein said vector is an adenovirus] wherein said vector is an adenoviral vector.